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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/225,426	01/05/99	ROSAZZA J	P00297US1

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EXAMINER	
SAUCIER,S	
ART UNIT	PAPER NUMBER
1651	18

DATE MAILED: 04/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/225,426	Rosazza et al.
Examiner	**Art Unit**
Sandra Saucier	1651

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 12, 2001*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3, 5, 6, 9-11, 13, 15, and 16* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, 5, 6, 9-11, 13, 15, and 16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claims 1, 3, 5, 6, 9-11, 13, 15, and 16 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The claims are examined to the extent that they read on peptides.

Please note that polyarginine and L-arginine cannot be considered to be peptides even with regard to the confusing and contradictory usages of the term, peptide, in the specification.

Claim Rejections - 35 USC § 112

NEW MATTER

Claims 1, 3, 5, 6, 9-11, 13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The independent claims 1, 10 and 16 now recite "from about 20-500 µg/kg of a peptide, oligopeptide or protein that acts as a substrate for or an inhibitor of nitric oxide synthase...".

There is some support for this recitation, but not for the breadth of this new limitation in the as-filed specification. The specification does not teach any and all modes of administration of 20-500 microg/kg of "active compounds", but only for intravenous administration of the "active compounds" as stated on page 36, l. 11.

The disclosure is narrower than the now pending claims.

Please see *Gentry Gallery v. Berkline* 45 U.S.P.Q.2d 1498 for a discussion related to broadening the claimed invention without support in the as-filed specification.

INDEFINITE

Claims 1, 3, 5, 6, 9-11, 13, 15 and 16 remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The specification has differing meanings for the term "peptide". On page 9, it reads "peptide is arbitrarily defined as a peptide chain having a single peptide bond". However, on pages 15 and 16, Table 1 and other places, peptide is used in its usual sense to mean a few amino acids linked with peptide bonds, such that bradykinin or a five amino acid sequence is called a peptide. The use of the term "peptide" is contradictory throughout the specification and the claims which leads to confusion as to the scope of the claims. Under one usage, no peptides are present in the Markush group, under another usage BK and its derivatives are peptides. Both contradictory usages appear to be supported by the specification.

Claims 3 and 13 are rejected because they are internally inconsistent and therefore, confusing. For example, L-arginine is cannot be considered to be a peptide, protein nor oligopeptide. Further, if the term "peptide" is used as on page 9 of the specification, claims 3 and 13 do not have a "peptide" in them either. The term "peptide" is not usually restricted to mean a dipeptide to one of skill in the art. Thus, the term "peptide" due to confusion in the specification, has been interpreted to have its usual meaning, that is a few amino acids linked by peptide bonds, in the interest of compact prosecution. Please resolve this continuing confusion.

Claims 3 and 13 also list "[Lys]-BK". Do applicants mean to cancel the material in the brackets? Is this meant to be BK or another derivative as suggested by the presence of the "-"? Please use the Seq. ID numbers.

Claims 3 and 13 use abbreviations. Does BK mean bradykinin? Does Met-Lys-BK mean that a methionine-lysine is attached to bradykinin? On which end are the two amino acids attached? Also, do the BK "fragments" refer to a Seq. ID number? If so, please use the Seq. ID numbers in the claims. Please try not to use abbreviations in the claims as abbreviations may be open to unfavorable interpretations.

Claim 3 and 13 are indefinite because the term, "polyarginine" does not designate a specific compound without an indication of molecular weight.

Claim 3 and 13 do not further limit the independent claim. Please note that BK fragment 2-7 has no arginine as required by the independent claim and that the arginine in Met-Lys-BK is not accessible to NO synthase as shown in Table 1.

Claim Rejections - 35 USC § 102

Claims 1, 5, 6, 10, 11, 15 and 16 remain/are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Groves *et al.* [V].

The claims are directed to a one step method of administering from 20-500 µg/kg of a peptide, oligopeptide or protein, containing an arginine available to NOS, to a mammal in order to regulate NO production.

Groves *et al.* disclose the one-step method of the administration of a regulator of NO production, HOE-140, a bradykinin B2 receptor antagonist to a human. This reference fulfills the one step method of administering a NO-regulating amount of an peptide. Bradykinin, an arginine containing peptide, stimulates the production of NO and vasodilation, while the peptide, HOE-140, which is a known bradykinin antagonist which contains arginine, limits NO production. The dosage is 200µg/min for 15mins. If one assumes that the average weight of a patient is 180 lbs, this is a dosage of about 36µg/kg, which is well within applicants' claimed range.

Response to Arguments

Applicants argue that Groves *et al.* teach that the administration of HOE-140 has no effect on NO on page 3429 of the reference. The reference states that "The fact that HOE-140 had no influence on NO synthase activity in cultured endothelial cells implies that its effects (*in vivo*) were not attributable to A NONSPECIFIC INHIBITION of enzymatic NO formation." Parenthetical insertion is mine. However, the effect of HOE-140 *in vivo* may have been as SPECIFIC inhibitor of NO formation. Please see page 3429, first paragraph where it is stated, "The vasodilatory actions of bradykinin are mediated largely through the stimulated release of NO,....and it is therefore likely that the actions of HOE 140 were to reduce the endogenous bradykinin stimulated release of one or more of these endothelium derived vasodilators. In other

words, the authors think that it is likely that HOE 140 is a bradykinin antagonist, which antagonists are suggested in the specification as NOS modulators.

In any case, the one step method of the claims is the same as the one step method of administering taught by the reference. The subject of the reference is the same as the subject of the claims, and all mammals are in need of prevention of disease. The dosage of the reference falls within the range of the dosage of the claims. The compound of the reference, HOE-140, is a peptide which contains at least one arginine at a terminus of the peptide. Thus, it is reasonable to conclude that the result of treating the same patient with a compound which falls within the definition of the claims and in within the same dosage of the claims would have the same effect as claimed.

In order to qualify as an anticipatory reference, the disclosure need not be express, but may anticipate by inherency. Failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation: In *Atlas Powder Co. v. IRECO, Inc.*, 51 USPQ2d 1943 (Fed. Cir. 1999).

See also, *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) The board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A US patent to Dart disclosed inoculation using *P. cepacia* bacteria for protecing the plant from fungal disease. Dart was silent with regard to nematode inhibition, but the Board concluded that nematode inhibition was an inherent property of the bacteria, and therefore of the method as disclosed by Dart.

Claims 1, 5, 9-11, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Thiemermann *et al.* [U].

The claims are directed to a one step method of administering from 20-500 µg/kg of a peptide, oligopeptide or protein, containing an arginine available to NOS, to a mammal in order to regulate NO production.

Thiemermann *et al.* disclose administration of 1-30mg/kg of NO_2-Arg-L-arginine and other dipeptides containing arginine, in vivo, to rats raises blood

pressure (vasoconstrictors). This is the same one step method as claimed.

Claims 1, 2, 5, 6, 10, 11, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by US 4585757 [A].

US 458575 discloses the administration of arginine containing peptides CIP fragment and contraceptive tetrapeptide in the range of 50-500 µg/kg to lower blood pressure (Table 3).

Claim Rejections - 35 USC § 103

Claims 1, 3, 5, 6, 9-11, 13, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4152425 [B].

US 4152425 discloses the infusion of 10-3000µg of kinin/l solution. The specifically preferred kinin is bradykinin. The infusion amount is exemplified at one liter (col. 5, l. 18).

The use of up to 3000µg/l/80kg = 37.5µg bradykinin/kg in the method of US 4585757 would have been obvious because this is within the range of administration of bradykinin taught in the art.

Claims 1, 5, 6, 9-11, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5648333 [C].

US 5648333 discloses the administration of the various peptides which are bradykinin antagonists in the range of 10µg-10mg/kg (Col. 18, l. 25 and Table 1).

Although the references are silent with regard to the effects of the administration of bradykinin or arginine containing peptides on NO production, it is reasonable to assume that the effects would be the same as claimed because, the patient is the same, the compounds administered are the same, the dosage is the same, the mode of administration is the same; therefore, the results would inherently be the same.

While discovery of the biological mechanism behind the administration of a known bioactive compound is clearly publishable in a peer-review journal, the criteria for patenting claims are distinct from publication criteria. For example,

if the active step of the method is the same and the subject is the same, then the claimed method can be anticipated or made obvious by the prior art, even if the prior art does not recognize or appreciate this mechanism as long as the compound administered, dosage, mode of administration, subject, etc. are the same as in the method disclosed in the prior art.

If this were not so, one patent might issue with a one step claim of administering the a compound to a subject in order to empirically treat a specific disease which is result of a contemporaneously unknown, disordered mechanism or pathway; and, then upon later discovery of the mechanism of the disorder, another patent could issue with a one step claim directed to the administration of the same compound to the same subject in order to modulate the specifically disordered mechanism or pathway. This would lead to multiple patents with essentially the same invention being patented, merely being couched in different words.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1651. The supervisor for 1651 is M. Wityshyn, (703) 308-4743.

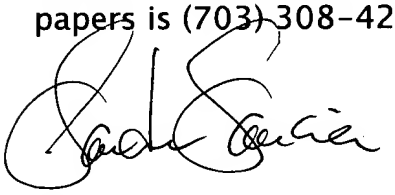
Conclusion

Applicant's amendment regarding range of dosage and other elements necessitated the new grounds of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone

number is (703) 308-1084. Status inquiries must be directed to the Service Desk at (703) 308-0196. The number of the Fax Center for the faxing of papers is (703) 308-4227.



Sandra Saucier
Primary Examiner
Art Unit 1651
April 17, 2001